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REVIEW

# Hematological manifestations of SARS-CoV-2 in children

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## Abstract

Infection from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), though mainly a respiratory disease, can impair many systems, including causing hematological complications. Lymphopenia and hypercoagulability have been reported in adults with coronavirus disease 2019 (COVID-19) and are considered markers of poor prognosis. This review summarizes the hematological findings in children with SARS-CoV-2 infection. The majority of infected children had a normal leukocyte count, while the most common white blood cell abnormality was leukopenia. Lymphopenia, which may be a marker of severe disease, was rarer in children than in adults, possibly due to their immature immune system or due to the less severe manifestation of COVID-19 in this age group. Age may have an impact, and in neonates and infants the most common abnormality was lymphocytosis. Abnormalities of red blood cells and platelets were uncommon. Anemia and hypercoagulability were reported mainly in children presenting the novel multisystem inflammatory syndrome (MIS) associated with SARS-CoV-2.

**KEYWORDS**
children, COVID-19, hematological manifestations, MIS, SARS-CoV-2

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on March 11, 2020, and cases of the disease are constantly increasing globally. Up until July 26, 2020, 15 785 641 cases and 640 016 deaths had been reported throughout the world.[1] The incidence is lower in children than in adults; the recent Morbidity and Mortality Weekly Report (MMWR) of the USA Centers for Disease Control and Prevention (CDC) showed that children accounted for 5% of the cases,[2] while an earlier report from the Chinese CDC reported that 2% of the cases were aged younger than 19 years.[3] Children tend to have a milder disease than adults,[4] but severe cases, deaths, and a novel multisystem inflammatory syndrome (MIS) have been reported in children following SARS-CoV-2 infection.[5,6]

A meta-analysis of clinical signs and symptoms in children and adolescents with COVID-19 showed that the most common symptoms were fever and cough, while a smaller percentage of children also had gastrointestinal symptoms such as diarrhea.[7] Although mainly a respiratory disease, COVID-19 is considered a multisystem disease and has multiple clinical manifestations.[8,9] In adults, the hematological complications that have been commonly reported include lymphopenia, which is associated with a worse clinical picture and poorer prognosis, and hypercoagulability, which is

**Abbreviations:** ACE2, angiotensin-converting enzyme 2; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; Hb, hemoglobin; ICU, intensive care unit; MAS, macrophage activation syndrome; MIS, multisystem inflammatory syndrome; NETs, neutrophil extracellular traps; PCR, polymerase chain reaction; RBC, red blood cell; SARS-CoV, severe acute respiratory syndrome coronavirus; SHLH, secondary hemophagocytic lymphohistiocytosis; WBC, white blood cell

  

associated with severe, often lethal complications.[10,11] The aim of this review was to summarize the data published to date on hematological manifestations in infants and children with SARS-CoV-2 infection.

## 2 | METHODS

Relevant papers on the hematological findings and complications of COVID-19 in symptomatic and asymptomatic children were identified through a PubMed search using the keywords "COVID-19," "SARS-CoV-2," "child," "laboratory findings," "hematologic complication," "thrombosis," "coagulopathy," "multisystem inflammatory syndrome," "patients with cancer," and "convalescent plasma" up to July 27, 2020. Only papers in the English language were reviewed. Meta-analyses and systematic reviews, observational cohort studies and case series were included, and case reports were used occasionally, when they described a rare but significant hematological manifestation. Articles were screened by title, abstract, and full text for hematological abnormalities, and the references were searched to identify additional studies. It should be noted that the same patients with COVID-19 may be reported in more than one available study.

### 2.1 | Abnormalities in the white blood cell count in children with COVID-19

Original studies published up to July 27, 2020[12–26] providing data on white blood cell (WBC) abnormalities in children with COVID-19 are shown in Table 1.

Raised leukocyte and neutrophil counts have been associated with unfavorable progression in adults.[27] Lymphopenia was detected in 80% of critically ill adults,[28] but in only 25% of adults with mild disease.[29] The proposed mechanism of lymphopenia includes the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed on the surface of lymphocytes.[11] The SARS-CoV-2 may directly infect lymphocytes via this receptor.[30] In critically ill patients, a systemic increase in cytokines and inflammatory mediators was demonstrated, which may result in marked lymphocytic apoptosis.[11,31,32]

A systematic review conducted in March by Henry and colleagues of the laboratory findings in 66 children with COVID-19, aged 6 weeks to 17 years, from 12 studies, found a normal leukocyte count in the majority of children. Lymphopenia was reported in only two infants (3%), neither of which had severe disease.[33] The authors suggested that the rarity of lymphopenia may be due to the less mature immune system of the children, which may respond differently to the SARS-CoV-2 infection than the mature system of adults. At a younger age, ACE2 is less developed, which may explain the infrequent occurrence of lymphopenia and the better COVID-19 prognosis.[7,34] This is further supported by the observation that a greater number of lymphocytes was associated with a shorter positivity period of viral nucleic acid, and thus faster virus clearance.[26]

Two more recent systematic reviews and meta-analyses confirmed the findings that most children with COVID-19 had a normal WBC count, and that the most common abnormality was leukopenia.[35,36] These reviews, however, provided no information on the association of the various WBC abnormalities (leukopenia, lymphopenia) with the disease severity or clinical course.

There is discrepancy among the available studies regarding the correlation of hematological manifestations with the severity of the disease in children. The association of lymphopenia with COVID-19 severity was documented in two studies from China, of 171[12] and 36[15] children, respectively. In a systematic review of 486 hospitalized children, the most common abnormalities detected in pediatric inpatients with COVID-19 were lymphocytosis (22%) and leukopenia (21%).[37] It should be noted that although these children were hospitalized, most had mild clinical manifestations, and the laboratory indicators and chest imaging features showed a milder disease than that reported in hospitalized adults.[37] In this meta-analysis, only 3% of the children had severe disease, which may explain the low incidence of lymphopenia.

Meta-analysis of data on 160 infants and neonates with COVID-19 from China and Vietnam showed that the most common laboratory findings were lymphocytosis, detected in 61% of the infants, and lymphopenia, detected in 16% of the infants and neonates. Infants and neonates appeared to present severe disease more commonly, as 7% were admitted to the intensive care unit (ICU) and one infant died.[38]

To summarize, the currently available data showed that the majority of children with COVID-19 had a normal WBC count, and that lymphopenia was rarer in children than in adults. Since lymphopenia appears to be associated with the severity of COVID-19 in adults, the absence of significant lymphopenia in children may be explained by the milder disease in this population. The most common WBC abnormality in children with COVID-19 was leukopenia, while in infants and neonates, lymphocytosis was more common. Finally, it appears that not only the clinical severity but also the age may have an impact on WBC in children with COVID-19.

### 2.2 | Abnormalities in the red blood cell count in children with COVID-19

Data on children with COVID-19 have, to date, shown no abnormalities in red blood cell (RBC) count or level of hemoglobin (Hb).[12–14,18] Hb levels were normal in asymptomatic children with COVID-19 but also in severe disease,[12,18] and did not differ between children admitted to the ICU or to a medical unit.[12–14] Anemia was a common feature in the children with a Kawasaki-like disease associated with SARS-CoV-2 infection, called multisystem inflammatory syndrome.[39] One case report described a 17-year-old male with a history of refractory chronic immune thrombocytopenia that manifested as autoimmune hemolytic anemia during infection with SARS-CoV-2.[40]

**TABLE 1** Studies on hematological laboratory findings in children with COVID-19, December 2019 to April 2020

| First author | Region | Study period | Number of children | Main hematological findings | | | |
|---|---|---|---|---|---|---|---|
| | | | | WBC | Hemoglobin | Platelets | D-dimer |
| Lu X, et al[12] | Wuhan Children's Hospital, China | January 28 to February 26, 2020 | 171 | Decreased in 26.3%<br>Lymphopenia in 3.5% (these children had either URTI or pneumonia) | Normal | | Increased D-dimer in 16% of children with URTI and 17.5% of children with pneumonia |
| Parri N, et al[13] | Italy, 17 pediatric emergency departments, the CONFIDENCE study | March 3-27, 2020 | 100 | Decreased in 17.7%<br>Lymphopenia in 28.5% | Normal | | |
| Chao J, et al[14] | Single tertiary children's hospital, New York City | March 15 to April 13, 2020 | 67 | Increased in children admitted to ICU | Mean 12.4 g/dL in patients admitted to ICU | Decreased in children admitted to ICU | Mean 0.8 $\mu$g/mL in patients admitted to ICU |
| Qiu H, et al[15] | 3 Hospitals, Zhejiang, China | January 17 to March 1, 2020 | 36 | Decreased in 19%<br>Lymphopenia in 31% | | | Increased D-dimer were associated with severity of COVID-19 |
| Xia W, et al[16] | Wuhan Children's Hospital, inpatients | January 23 to February 8, 2020 | 20 | Normal in 70%<br>Decreased in 20%<br>Increased in 10%<br>Lymphopenia in 35% | | | |
| Zheng F, et al[17] | 10 Hospitals, Hubei, China | February 1-10, 2020 | 25 | Lymphopenia in 40% | | | |
| Sun D, et al[18] | ICU of Wuhan Children's Hospital, China | January 24 to February 24, 2020 | 8 | Normal or increased | Decreased in 3 children | $<100 \times 10^9$/L in 1 patient | Increased in 2 children |
| Liu W, et al[19] | 3 Branches of Tongji Hospital, Wuhan, China | January 7-15, 2020 | 6 | All had lymphopenia | Decreased in 1 patient | Normal | Increased in 3 children |
| Zheng G, et al[20] | 11 Hospitals from South China | January 21 to February 29, 2020 | 52 | Decreased in 6%<br>Lymphopenia in 6%<br>Lymphocytosis in 46.2% | | | |
| Romani L, et al[21] | 1 Hospital, Italy | March 15 to May 6, 2020 | 43 | Lymphopenia in 37%<br>Neutropenia in 26% | | Transient and self-limited thrombocytopenia ($112 \times 109$/L) in 1 child with respiratory deterioration | |

(Continues)

**TABLE 1** (Continued)

| First author | Region | Study period | Number of children | Main hematological findings | | | |
|---|---|---|---|---|---|---|---|
| | | | | WBC | Hemoglobin | Platelets | D-dimer |
| Chen Z, et al[22] | 7 Hospitals in Zhejiang province, China | January 15 and March 15, 2020 | 32 | Normal | | | |
| Bhumbra S, et al[23] | Riley Hospital for Children, Indianapolis, USA | February 26 to May 4, 2020 | 19 | Median 5700/mm$^3$ in critically ill Median 8500/mm$^3$ in general ward | | Thrombocytopen in 66% of critically ill patients 0% In general ward | |
| Zhang L, et al[24] | 10 Hospitals in Anhui, China | December 2019 to February 2020 | 33 | Lymphopenia in 75.7% | | | |
| Korkmaz M, et al[25] | Bursa City Hospital, Turkey | March 5 to May 5, 2020 | 79 | Lymphopenia in 2.5% Leukopenia in 5%, | | Normal | Increased in 12.3% |
| Xu H, et al[26] | 4 Provinces in Western China | January 24 and February 12, 2020 | 32 | Significant negative correlation between lymphocyte count and the time until the first negative nucleic acid, after adjusting for age, gender, and length of stay | | | |

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; URTI, upper respiratory tract infection; WBC, white blood cell.

## 2.3 | The risk of thrombotic complications in children with COVID-19

In adulthood, COVID-19 creates a hypercoagulability state that leads to thrombotic complications, which are associated with a poor prognosis.[41] The pathophysiology of COVID-19-induced coagulopathy has not been clarified, but the hypothesis is that overactivation of the complement system contributes to a thrombotic tendency.[42] SARS-Cov-2 is an RNA virus, and extracellular RNA has been identified to be both a natural factor VII-activating protease cofactor,[43] and a natural procoagulant cofactor, by increasing the autoactivation of proteases of the intrinsic pathway of blood coagulation, such as factors XII and XI.[44] Antiphospholipid antibodies may also play a role in COVID-19-associated thrombosis.[45] Neutrophil extracellular traps (NETs), which are extracellular networks of chromatin and nuclear and antimicrobial proteins, are released by neutrophils to restrain infections. NETs can initiate and provoke inflammation and thrombosis by activating extrinsic and intrinsic pathways, and by trapping and activating platelets.[46–48] In hospitalized adult patients with severe COVID-19, the serum concentration of NETs was found to be increased.[49] Finally, endotheliitis, which has been described in patients with COVID-19, could also explain the hypercoagulability state associated with this infection. Specifically, ACE2 receptors are expressed in vascular endothelium, rendering the endothelium vulnerable to diffuse infection, injury, and dysfunction.[48,50]

Raised levels of D-dimers and fibrinogen degradation products were shown to be associated with critical illness and mortality from COVID-19, and an elevated level of D-dimers at admission was an independent prognostic factor of in-hospital death in adults.[51,52] The incidence of thrombotic complications in adults with severe disease was 31%,[53] and in an autopsy study, venous thromboembolism was found in 40% of cases.[54]

The scarcity of data regarding thrombotic complications in children with COVID-19 suggests that such complications may be rare in childhood. Recently published anticoagulation recommendations for children support the evaluation of children with SARS-CoV-2 infection for thrombosis, not only at admission but daily during hospitalization.[55] Because of the multiple risk factors, administration of prophylactic

anticoagulant therapy for children is recommended only after careful consideration of each child's bleeding risk.[55]

COVID-19 may cause disseminated intravascular coagulation in adult patients, with a mild decrease in platelet count and mild prolongation of partial thromboplastin time, but no signs of microangiopathy.[55] Meta-analysis of 551 pediatric cases showed that the prevalence of raised D-dimers was 12%, but there was no mention of thrombotic adverse events in the children.[24] In the study of Lu and colleagues, the children had normal thrombin and prothrombin time and normal fibrinogen levels. Raised levels of D-dimers were found in 17.5% of children with pneumonia and 16% of children with upper respiratory tract infections, but not in asymptomatic children.[12] Thrombocytopenia has been associated with respiratory deterioration in children,[21] more often encountered in critically ill patients and those admitted to the pediatric ICU.[14,23]

## 2.4 | MIS in children with COVID-19

The original studies[5,39,56–64] on the laboratory findings on children with MIS during the COVID-19 pandemic are shown in Table 2. Recently, SARS-CoV-2 has been associated with a novel MIS in children, with signs and symptoms resembling those of Kawasaki disease.[60] In a large cohort of 186 children from 26 States in the United States, this syndrome involved multiple systems: gastrointestinal in 92%, cardiovascular in 80%, hematological in 76%, mucocutaneous in 74%, and respiratory in 70%.[56] The children with MIS have raised serum levels of inflammatory markers, and specifically interleukin-6 (IL-6) and C-reactive protein (CRP). They have a raised erythrocyte sedimentation rate (ESR), and high levels of serum ferritin, procalcitonin, brain natriuretic peptide, and troponin.[39,58,65] The majority of children with MIS had neutrophilia, lymphopenia, anemia, thrombocytopenia, and raised levels of D-dimers, with a prolonged international normalized ratio (INR) or raised fibrinogen level.[39,56]

These laboratory findings are suggestive of a "cytokine storm,"[58] similar to that reported in adults, but the presentation of MIS has been delayed until after the peak of SARS-CoV-2 cases in each city where it has been reported.[66] It is therefore considered to be an immunologically mediated inflammation syndrome, associated with an earlier SARS-CoV-2 infection.[60,67] In the study of Belhadjer and colleagues, antibody assays were positive in 86% of the cases of MIS, and IgG type antibodies were already detectable, suggesting an older SARS-CoV-2 infection, while 34% had a positive nasopharyngeal polymerase chain reaction (PCR) test for SARS-CoV-2, and 6% had positive fecal PCR.[58] This Kawasaki-like disease is considered to be mediated by proinflammatory cytokines produced by macrophages and mast cells.[68]

In the available reports, the features of MIS resemble those of secondary hemophagocytic lymphohistiocytosis (SHLH)/macrophage activation syndrome (MAS). Hemophagocytic lymphohistiocytosis (HLH) is characterized by a similar pathogenesis of cellular activation leading to a "cytokine storm" with raised levels of proinflammatory cytokines.[65,69] SHLH can be triggered by viral infections,[70] and findings in patients include fever, hyperferritinemia, high levels of inflammatory markers, and evidence of organ dysfunction.[71] Hyperferritinemia (>500 ng/mL), which is a red flag finding for SHLH/MAS, is yet not pathognomonic for MIS, but was detected in six of eight patients hospitalized in a pediatric ICU in London during the COVID-19 pandemic.[61] In Bergamo province in Italy, among 10 children who presented with Kawasaki-like disease during the SARS-CoV-2 pandemic, five were diagnosed with MAS.[60]

## 2.5 | Convalescent plasma treatment and its effect on hematology parameters

Currently, many treatment agents against COVID-19 are being evaluated. The plasma from patients who have recovered from COVID-19 infection, named convalescent plasma, has been evaluated as a potential tool against COVID-19, since this treatment strategy has been used successfully for other diseases in the past.[72–74] The use of convalescent plasma was approved by the US Food and Drug Administration (FDA) in March 2020 for use in patients with serious or life-threatening COVID-19, and FDA has issued instructions on the criteria for eligible donors and recipients.[75] A recent comprehensive literature review discussed all the current studies and clinical trials of convalescent plasma use in patients with COVID-19.[72] Although positive outcomes were reported in many studies,[72] a randomized controlled trial conducted in Wuhan, China found no significant improvement in time to clinical improvement with convalescent plasma therapy in adults.[76] One case has been reported of convalescent plasma use in a 6-year-old girl with severe COVID-19 who presented with aplastic anemia and severe pancytopenia. In spite of administration of antiviral drugs and immune modulators, the SARS-CoV-2 RNA test remained positive for 5 weeks. After use of convalescent plasma, the SARS-CoV-2 RNA test turned negative, but the hematological parameters did not improve after SARS-CoV-2 elimination.[77] There is also a recent report of convalescent plasma being safely administered to four critically ill children aged 14–18 years. An encouraging clinical response was observed in one patient, who had received plasma with a high antibody titer.[78]

## 2.6 | COVID-19 infection in pediatric oncology patients

Respiratory viral infections are the most significant cause of acute respiratory tract infections in pediatric patients with cancer, and an important cause of febrile neutropenia and hospital admission in this population. Pediatric patients with cancer are at a higher risk of life-threatening complications from respiratory viral infections and their incidence of coinfection is higher than that of the general pediatric population.[79]

While several reports have documented that adult oncology patients are at higher risk of complications from COVID-19 than those without cancer,[80,81] the impact of SARS-CoV-2 on children with malig-

**TABLE 2** Studies on hematological laboratory findings of multistystem inflammatory syndrome in children associated with SARS-CoV-2 (February-June 2020)

| First author | Region | Study period | Number of children | Main hematologic findings | | | |
|---|---|---|---|---|---|---|---|
| | | | | WBC | Hemoglobin | Platelets | Coagulation studies |
| Feldstein LR, et al[56] | Pediatric health centers across 26 US States | March 15 to May 20, 2020 | 186 | Neutrophilia Lymphopenia | Anemia | Thrombocytopenia | Increased D-dimers Prolonged INR Increased fibrinogen level |
| Duforf E, et al[57] | Hospitals in New York | March 1 to May 10, 2020 | 95 | Lymphopenia in 66% | | | Increased D-dimers in 91% |
| Davies P, et al[62] | Pediatric ICUs in United Kingdom | April 1 to May 10, 2020 | 78 | Lymphopenia at admission, but median lymphocyte count was normal on day 3 Neutrophilia | | Thrombocytopenia at admission, but median platelet count was normal on day 3 | Increased D-dimers |
| Whittaker E, et al[5] | 8 Hospitals in England | March 23 to May 16, 2020 | 58 | All had neutrophilia | | | |
| Belhadjer Z, et al[58] | 14 ICUs in France and Switzerland | March 22 to April 30, 2020 | 35 | Leukocytosis Neutrophilia | | | Increased D-dimers |
| Toubiana J, et al[39] | University Hospital in France | April 27 to May 11, 2020 | 21 | All had leukocytosis, neutrophilia Lymphopenia in 81% | Anemia | | Increased D-dimers in 95% |
| Cheung E, et al[59] | Children's Hospital in New York City | April 18 to May 5, 2020 | 17 | Most had lymphopenia and bandemia | | | |
| Verdoni L, et al[60] | Bergamo province, Italy | February 18 to April 20, 2020 | 10 | The majority had neutrophilia, lymphopenia 5 Children had macrophage activation syndrome | | Thrombocytopenia | Increased D-dimers |
| Riphagen S, et al[61] | ICU, UK | 10 Days in mid-April, 2020 | 8 | | | | Increased D-dimers |
| Moraleda C, et al[63] | 49 Hospitals in Spain The Epidemiological Study of COVID-19 in Children of the Spanish Society of Pediatrics (EPICO-AEP) | March 1 to June 1, 2020 | 31 | | | | Increased D-dimers in 97% |
| Lee P, et al[64] | Boston Children's Hospital, USA | March to June, 2020 | 28 | Lymphocytopenia in 75% All patients had at least one inflammatory marker increased | | Thrombocytopenia in 64% | Increased D-dimers in 96%, and 62% had prolonged prothrombin time |

Abbreviations: ICU, intensive care unit; SARS-CoV, severe acute respiratory syndrome coronavirus; WBC, white blood cell.

nancies is poorly documented. Five pediatric oncological patients with COVID-19 in Italy presented a benign self-limiting course.[82] Up until mid-April, 14 pediatric patients with cancer were reported in Italy, all with a favorable clinical course.[83] A retrospective study of pediatric hematology and oncology patients in New York City reported that most presented symptomatic disease, most commonly fever, cough, and dyspnea, and of 19 patients, five, all males, required hospitalization in the ICU.[84] In a study from Peru, almost half of 69 pediatric patients with cancer presented asymptomatic SARS-CoV-2 infection.[85] The most common clinical manifestations in symptomatic infection were fever and cough.[85,86] The authors commented that from current evidence, pediatric patients with cancer do not appear to have a higher mortality rate from SARS-CoV-2 infection, although these patients may have a worse outcome in low- and middle-income countries.[85] In a study of 15 children from Madrid, 73% with hematological malignancies and 27% with solid tumors, the median WBC count at COVID-19 diagnosis was 3195/mm$^3$ (range 90-10 690), the median lymphocyte count was 580/mm$^3$ (range 0-6310), and the median D-dimer level was 291 ng/mL (range 0.7-2620). All the patients had a favorable clinical outcome.[86] There have also been reports of children with malignancy presenting severe respiratory distress and significant hyperinflammation, requiring ICU care and COVID-19 treatment.[87,88]

## 3 | CONCLUSIONS

Although in adults with COVID-19 disease, hematological manifestations have been commonly documented, with prognostic significance, in children this was not so evident. In adults with severe disease, lymphopenia is a frequent finding, and leukocytosis with neutrophilia is considered an unfavorable parameter. Leukocyte changes, and especially lymphopenia, were less commonly documented in children with COVD-19, possibly because of their immature immune system and ACE2 expression. When hematological abnormalities were detected in children with COVID-19, leukopenia was the most common finding. Lymphopenia was found mainly in hospitalized older children. In neonates and infants with COVID-19, the most common hematological abnormality was lymphocytosis. Thus, in children, not only the clinical severity but also the age may have an impact on the WBC. Anemia and thrombocytopenia were rarely found in children with COVID-19. In adults, SARS-CoV-2 infection is often associated with major blood hypercoagulability, but in children this was a rare complication, which occurred mainly in the setting of the novel MIS.

Data on the epidemiology, clinical manifestation, and optimal management of SARS-CoV-2 infection in children with malignancies are currently limited. National and regional guidelines must be followed strictly to minimize exposure and to avoid delays in cancer treatment.

### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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